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Neuropsychological deficits in young drug addicts

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Summary

Background: Adolescence is a highly vulnerable age for experimenting with drugs; increasing evidence attests that several substances might have detrimental effects on cognitive functioning in this developmental phase, when prefrontal brain areas are still immature and may actually be the main target of the neurotoxic effects of drugs. There are still, in any case, too few studies that specifically address early adulthood. **Aim:** The present study aims to investigate neuropsychological performance in young drug addicts in residential treatment (aged 18-24). **Methods:** 41 young drug addicts, after admission to residential treatment, were compared with 27 subjects in the control group. A battery of neuropsychological tests (Brief Neuropsychological Exam-2) was administered to detect possible cognitive impairments. Descriptive and non-parametric statistics (Pearson's chi square test) were performed. **Results and conclusions:** Findings suggest that drug dependence in youth is distinguished by neuropsychological deficits, in particular, attention and executive function impairments – issues that now call for tailored and innovative treatment approaches.

Key Words: Emerging adulthood; drug addiction; neuropsychological functioning

1. Introduction

It is widely acknowledged that drug abuse has a neurotoxic effect on several brain circuitries that leads to structural and functional changes, mainly in the dopaminergic mesolimbic system of reward, but that also causes a cascade of neuroadaptations [52]. Consistent empirical evidence establishes that the structural and functional changes consequent on prolonged substance abuse mediate severe neuropsychological deficits; this has been attested even in adolescence and youth [11, 31], since important neuromaturation processes take place during the developmental period and continue until emerging adulthood [13, 23, 24], making the adolescent brain particularly vulnerable to disruptive factors.

The exposure to neurotoxins that is introduced through the use of alcohol and drugs exerts an adverse influence on the structural and functional development of the brain, especially at the expense of the corpus callosum, hippocampal and prefrontal cortex regions [62], so leading to neuropsychological impairments that primarily affect memory, attention and executive functions, often exerting a long-term influence [58]. It is, in any case, important to mention the need for caution in interpreting these results: the causal and temporal relationships between prior risk factors, substance abuse, and cognitive deficits still have to be determined, whereas it can be assumed that neuropsychological impairments pre-exist, exacerbate, and/or follow substance use [62].

Alcohol Use Disorders (AUDs) in adolescence and emerging adulthood are associated with deficits in several cognitive domains, and predict an increase in impulsive behaviour [35]. Impairments have been demonstrated for verbal and non-verbal memory [9],

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attention [57], processing speed [38], visuospatial abilities [27], executive functions [22], and language skills [45].

With regards to the neuropsychological consequences of cannabis use, it has been posited that the domains of psychomotor speed, attention [34, 59], memory [5, 59], cognitive inhibition [34], verbal learning, spatial working memory [28], and executive functions [25, 51, 54] are all affected.

Cocaine-abusing adolescents have shown impairments in executive control, attention, cognitive abstraction processes, visuospatial skills, psychomotor speed, and short-term memory [4, 10, 30, 55, 63].

Apart from the above substances, nowadays, ketamine (N-methyl-D-aspartic acid; NMDA), one of the most common NMDA receptor antagonists, is a mainstream club drug. Both a large-scale study [43] and longitudinal research [44] conducted on young adults have demonstrated cognitive impairments in high-frequency users, at the expense of memory and planning functions, and they have also detected an association between the trend of ketamine use over time and a worsening of neuropsychological performance. Moreover, the use of MDMA during the teens and young adulthood leads to diminished performance over time in coping with complex, divided, and selected attention and memory tasks, so causing significantly prolonged reaction times [29]. In responding to a battery of neuropsychological tests, young users of MDMA and cannabis display cognitive impairments in performing a number of cognitive tasks (memory, learning, speed of processing) [14].

Several studies have focused on opioids and heroin. According to Davis et al. [15], 60% of opiate users show neuropsychological impairments, even though it is not clear if the deficits found are focal or diffused. It is primarily memory and the spectrum of executive functions that appear to be impaired [61, 60], involving deficits in impulse control, planning, problem solving, and implying a characteristic perseverative behaviour pattern [17, 18, 36, 46, 49]. Prefrontal cortex and limbic abnormalities have been detected in this population [17, 33, 50]. Many studies on opioid dependence have also investigated deficits in decision-making abilities, a cognitive domain that combines executive and emotional components, indicating an impaired performance in opioid users, in terms of risky decisions that have negative long-term consequences [7, 17, 20, 61]. As it is, the studies available so far have almost exclusively addressed the performance of adults, so that further evidence specifically addressed to adolescent and emerging adulthood is needed.

Other studies have addressed polydrug use. Adolescents who abuse multiple drugs show impairments in executive control, attention, abstract reasoning, visuospatial capabilities, psychomotor speed, and short-term memory performance [58]. Adolescent polyusers of alcohol and marijuana performed significantly worse than controls on cognitive tests regarding intellectual capacity, perceptual speed, language and attention [57].

The existing literature mainly focuses on adolescence or full adulthood, while it is limited on emerging adulthood. Moreover, there are still too few studies on groups of individuals whose SUD rises to a level of severity that requires inpatient treatment, and this is particularly true of the Italian context. The purpose of the present preliminary study was to investigate the neuropsychological profile of young, drug-dependent inpatients who started abusing drugs in adolescence, in order to determine if they might be suffering from cognitive impairments.

2. Methods

2.2. *Sample*

The present research initially involved 68 people emerging into adulthood, aged 18-24, divided into a clinical group and a comparison group. The collection of clinical data occurred as part of a broader research project (Psychological Assessment & Treatment With Addicted Youth [P.A.T.W.A.Y.]).

The clinical group was recruited in the years 2013-2015 in a residential Therapeutic Community for Substance Use Disorders named “Villa Renata, Comunità di Venezia,” located in Venice, Italy. The following inclusion criteria were adopted: a) meeting DSM-IV-TR [1] criteria for Substance Use Disorder; b) being referred to, and then admitted to the residential treatment community for less than 3 months; c) age ranging from 18 to 24 years. The administration of the assessment tools occurred approximately 2 months after their admission (M=1.4 months). 41 young inpatients took part in the study. As regards participants’ past history of drug use, as a general rule they first experimented with drugs (often, but not exclusively, with alcohol and marijuana) in early adolescence (on average at 14 years), while the onset of cocaine and heroin use occurred on average at 16 years (± 1.9). Most of them were polydrug users (80.5%), using various synthetic drugs (78%), but they indicated heroin as their primary substance of abuse in 75.6% of cases. In addition, the use of non-prescribed drugs is quite common, with 51.2% of these subjects having used methadone procured illegally. At the time of recruitment, participants had been abstinent from drugs for 3 months on average, as verified by urine tests. 46.6% overdosed from one to three times in the past and 24.4% had been diagnosed with hepatitis C. None of them presented other relevant medical conditions, or any other full-blown psychiatric disorders apart from SUD. In relation to treatment, the participants' first contact with outpatient services for SUDs occurred on average at 18 years (± 2.3), that is, about two years after initiating the use of hard drugs such as heroin and cocaine. 41.5% of them had previously attended an inpatient treatment but had not concluded it. Pharmacotherapy (mainly benzodiazepines, SSRI, neuroleptics) was prescribed for most of them (84.2%).

The comparison group included 27 young people, who had been contacted as students of evening or day high schools. The main selection criteria used in the collection of these data were a) the absence of SUDs diagnosis and current drug use; b) age in the 18-24 range; c) low educational level; d) gender, in order to collect a comparison group as closely comparable as possible with the clinical one. These criteria were established primarily according to indications provided for the assessment of neuropsychological functioning, whose normative range depends on age and years of education.

2.3. Instruments

The collection of sociodemographic and drug history data was performed by applying an ad hoc interview format that conforms to the standard protocol adopted by the Therapeutic Community for all patients at admission. When necessary, data were integrated and/or confirmed by information reported in records provided by the outpatient mental health services that referred the patient to the facility.

A neuropsychological assessment protocol was administered individually to each participant; it usually took about an hour and a half.

Esame Neuropsicologico Breve-2 [Literal translation: Brief Neuropsychological Examination-2] (ENB-2; [41]), which is a comprehensive neuropsychological battery standardized for the Italian population. It includes 16 subtests (Digit span, Immediate and delayed recall prose memory, Interference memory at 10 and 30 seconds, Trial Making Test part A and B, Token test, Word phonemic fluency, Abstract reasoning, Cognitive estimation, Overlapping figure, Spontaneous drawing, Copy drawing, Clock drawing and Ideative/ideomotor praxis tests). The ENB-2 allows us to investigate several cognitive abilities: attention (TmtA, TmtB), memory (digit span, logic story-immediate recall, logic story-delayed recall, interference memory at 10- and 30-second tests), executive functioning (TmtB, cognitive estimation, abstract reasoning, phonemic fluency, clock drawing, overlapping figures), perception (spontaneous drawing, copy drawing), praxis abilities (ideative and ideomotor praxis test) and comprehension (token test). The battery provides a score for each cognitive test and a total score too, called the Global Cognitive Index. Age (15–20, 21–30 years) and education (lasting less than 9 years and at least 9 years) are the two criteria used to identify subgroups of individuals and their respective normative scores. The 5th percentile was used to determine cut-off scores for each subgroup; according to the cut-off score, performance is classified as belonging to one of the three categories: below average, borderline and above average. The battery shows good psychometric characteristics, revealing good differential validity in discriminating normative and clinical groups and sufficient test-retest reliability [42].

2.5. Data analysis

Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) 21.0. Qualitative analysis was carried out using descriptive statistics, while for the quantitative analysis, due to the small number of subjects, non-parametric tests were applied (Pearson's chi square test).

3. Results

Inpatients were 53.7% males (N=22) and 46.3.% (N=19) females; the mean age was 20.9 years (± 2.2). 10 years (± 1.8) was the average duration of school attendance in this group; moreover, 80.5% had repeated at least one grade at school and, more interestingly, 73.2% had dropped out of school before concluding compulsory education. A majority of participants were unemployed (63.4%) and were relying on illegal activities to provide their main economic support, often incurring legal injunctions. One or both parents of many young inpatients (48.8 %) had themselves been affected by a past or current Substance Use Disorder, besides which 38.5% had been exposed to alcohol or drugs when still in the womb. In addition, as re-

Table 1. Percentages of patients with neuropsychological deficits

Cognitive domain	Drug addicts			Non-drug			Chi squared Test	
Test	Limit %(N)	Impaired %(N)	Altered % (N)	Limit %(N)	Impaired %(N)	Altered % (N)	χ^2	P
Attention								
TMT-A	-	22 (9)	22 (9)	-	-	-	6.831	.000
TMT-B	2.4 (1)	53.7 (22)	56.1 (23)	-	11.3 (3)	11.3 (3)	13.951	.000
Memory								
Digit span	-	4.9 (2)	4.9 (2)	-	14.8 (4)	14.8 (4)		
Immediate recall	9.8 (4)	36.6 (15)	46.3 (19)	3.7 (1)	33.3 (9)	37.0 (10)		
Delayed recall	4.9 (2)	26.8 (11)	31.7 (13)	11.1 (3)	22.2 (6)	33.3 (9)		
Interference memory 10s	22.0 (9)	12.2 (5)	34.1 (14)	18.5 (5)	22.2 (6)	40.7 (11)		
Interference memory 30s	12.2 (5)	12.2 (5)	24.4 (10)	11.1 (3)	11.1 (3)	22.2 (6)		
Comprehension								
Token test	-	7.3 (3)	7.3 (2)	-	-	-		
Executive Function								
TMT-B	2.4 (1)	53.7 (22)	56.1 (23)	-	11.3 (3)	11.3 (3)	13.951	.000
Cognitive estimation	22.0 (9)	19.5 (8)	41.5 (17)	33.3 (9)	18.5 (5)	48.1 (13)		
Abstract reasoning	12.2 (5)	9.8 (4)	22.0 (9)	11.1 (3)	3.7 (1)	14.8 (4)		
Phonemic fluency test	9.8 (4)	14.6 (6)	24.4 (10)	11.1 (3)	29.6 (8)	40.7 (11)		
Clock Drawing test	7.3 (3)	29.3 (12)	36.6 (15)	7.4 (2)	3.7 (1)	11.1 (3)	5.428	.025
Overlapping figures	4.9 (2)	9.8 (4)	14.6 (6)	-	-	-		
Perception								
Spontaneous drawing	-	2.4 (1)	2.4 (1)	7.4 (2)	3.7 (1)	11.1 (3)		
Copy drawing	2.4 (1)	22.0 (9)	24.4 (10)	3.7 (1)	7.4 (2)	11.1 (3)		
Praxis Ability								
Ideomotor praxis	-	2.4 (1)	2.4 (1)	-	-	-		
Global Index	9.8 (4)	46.3 (19)	56.1 (23)	-	18.5 (5)	18.5 (5)	9.491	.003

Note: altered comprehension limit and impaired performance.

gards the childrearing environment in which they had grown up, a high percentage (53.7%) had experienced maltreatment, including sexual or physical abuse during childhood and/or adolescence.

The group of young non-addicts included 37% males (N=10) and 63% females (N=17), whose mean age was 19.44 (±1.9). As regards education, the mean duration of school attendance was 10.44 years (±1.2) at the time of assessment, with 66.7% of individuals who had not yet completed compulsory education, reporting middle school as their final educational level.

The neuropsychological performance of participants on the ENB-2 battery was codified into 3 categories (below average, borderline and average); in addition, a fourth, 'altered' category was computed, to include subjects whose performance was at the limit or definitely impaired.

As reported in Table 1, results showed that 56% of drug-dependent patients had an impaired global cognitive profile at ENB-2, considering both those whose Global Cognitive Index reached the limits of expected levels and those who had fully impaired neuropsychological functioning. Observing the performance on the single tasks included in the battery, a high percentage of young inpatients showed an impaired performance in carrying out the following tasks: Tmt-B (56%), memory task Logical Story – Immediate Recall (46.3%), Cognitive Estimation Test (41.5%) and, even if to a lesser extent, the task called Clock Drawing (36.6%), Interference memory at 10 seconds (34.1%) and Logical Story – Delayed Recall (31.7%).

From a qualitative perspective, the neuropsychological performance of the majority of individuals in the comparison group (81.5%) fell into the normative range for age and education. Nevertheless, some cognitive tasks showed quite high rates of individuals who gave an altered performance, namely in carrying out the Cognitive Estimation (48.1%), Phonemic Fluency and Interference Memory tests in 10 seconds

(40.7%).

Pearson's chi square test reported a statistically significant difference between the two groups for Tmt-A (χ^2 = 6.831, p = .000), Tmt-B (χ^2= 13.951, p=.000), Clock Drawing Test (χ^2=5.428, p=.025) and Global Cognitive Index (χ^2=9.491, p=.003); these results were confirmed by the Bonferroni post-hoc test (p=.05/4=.012) for all tasks except for Clock Drawing Test. Data indicated that a higher percentage of youth with drug-addiction problems had an impaired global cognitive profile than their peers without SUDs. In particular, drug addicts showed a higher level of difficulty in the attention (Tmt-A, Tmt-B) and executive functions, specifically the attentive (Tmt-B) domain.

4. Discussion and conclusions

This preliminary study has been designed as a contribution to the knowledge of drug addiction in young adulthood, in particular, to a better understanding of neuropsychological functioning in inpatients aged 18-24.

Our examination of participants' neuropsychological functioning highlighted the fact that a high proportion of young drug-dependent individuals, who were mainly heroin-addicted, showed an impaired cognitive profile, to a greater extent than their peers in the comparison group. From a focal perspective, neuropsychological impairments occurred mainly at the expense of attention and executive functions assessed with Tmt-A and Tmt-B. The latter is widely used as a measure of cognitive flexibility; it provides information about the speed of processing and executive functioning, as well as complex, divided and selected attention [3]. Results are in line with the empirical evidence presented above, which recognizes an association between cognitive deficits and the misuse of several different drugs [e.g. 14, 18, 44, 54, 63], even if empirical evidence on young opioid users is very limited, particularly in the Italian context.

Given the absence of a perspective design, no assumptions should be made about the origins of these deficits, which may either be subsequent to substance abuse or pre-existing it, or be related to other previous clinical/risk conditions, such as Attention Deficit Hyperactivity Disorder (ADHD) and intrauterine drug exposure, [21, 32, 40, 53]. It is noteworthy that a considerable number of young people in the comparison sample showed an altered level of performance in a few tasks, namely the Cognitive Estimation test (designed to assess the capacity to answer a question for which relevant knowledge, but not the specific answer, is available) and Phonemic Fluency (a task involving vocabulary size, lexical access speed, updating, and inhibition ability) as regards executive function, and Immediate Recall and Interference memory at 10 seconds as regards memory abilities. These data could be explained by considering in greater depth other variables, such as socioeconomic status, rearing environment and traumatic experiences, which are capable of compromising optimal cognitive functioning, [6, 16, 19, 26, 39, 47], besides individual and sociorelational adjustment [13, 23, 12, 56]. Moreover, other methods of drug testing would provide more reliable information about drug use than self-reported answers [37].

Intact cognitive abilities, in particular executive functions, are crucial for a goal-directed and controlled behaviour that underpins individual adjustment. In the case of drug addiction, growing evidence indicates that cognitive impairments may negatively affect treatment [48], and may be long-lasting. Even after long-term recovery, the cessation of drug use is unable to fully restore cognitive functioning [54, 27; 58], and impairments are detected even after years of abstinence from opioids [7, 18]. Thus, restoring and potentiating these abilities in drug addicts, especially if they are young, emerges as a priority. In fact, developmental neuroscience reports that the brain developmental changes are not fully completed until reaching the age of approximately 25 years, in particular in the prefrontal cortex areas, so offering a window of intervention opportunity [62, 2]. Thus, neuropsychological rehabilitation may be considered as an additional treatment to traditional protocols (based on educational and psychotherapeutic interventions) provided to young drug addicts, who would then be placed in the position to fully benefit from standard programmes. This might help in counteracting the present worrying levels of treatment dropout and poor outcome [8]. Unfortunately, despite the recognition of their importance, cognitive abilities play a peripheral role in clinical practice and, to date, only a few studies have been made available on the ideation and implementation of treatment programmes that address the issue of cognitive impairments in the population of drug addicts, which now call for further research [18].

The preliminary nature of the research and the small size of its samples are the main limitations of the study, imposing caution in drawing conclusions. The high degree of specificity of the clinical sample – made up of young adults whose SUDs was severe enough to require inpatient treatment – can be considered both as a source of strength and as a limitation of the study. Moreover, as mentioned earlier, the study does not allow any speculation about temporal sequencing and causality between drug misuse and neuropsychological phenomena.

References

1. American Psychiatric Association. (2000): *DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision*. American Psychiatric Association. Washington, D.C.
2. Arain M., Haque M., Johal L., Mathur P., Nel W., Rais, A., Sandhu, R., Sharma, S. (2013): Maturation of the adolescent brain. *Neuropsychiatr Dis Treat*. 9: 449-461.
3. Arbuthnott K., Frank J. (2000): Trail making test, part B as a measure of executive control: Validation using a set-switching paradigm. *J Clin Exp Neuropsychol*. 22(4): 518-528.
4. Bartzokis G., Beckson M., Lu P. H., Edwards N., Bridge P., Mintz J. (2002): Brain maturation may be arrested in chronic cocaine addicts. *Biol Psychiatry*. 51(8): 605–611.
5. Becker B., Wagner D., Gouzoulis-Mayfrank E., Spuentrup E., Daumann J. (2010): The impact of early-onset cannabis use on functional brain correlates of working memory. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 34(6): 837-845.
6. Bennett D. S., Bendersky M., Lewis M. (2008): Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence. *Dev Psychol*. 44(4): 919.
7. Brand M., Roth-Bauer M., Driessen M., Markowitsch H. J. (2008): Executive functions and risky decision-making in patients with opiate dependence. *Drug Alcohol Depend*. 97(1-2): 64-72.
8. Brorson H. H., Arnevik E. A., Rand-Hendriksen K., Duckert F. (2013): Drop-out from addiction treatment: A systematic review of risk factors. *Clin Psychol Rev*. 33(8): 1010-1024.
9. Brown S. A., Tapert S. F., Granholm E., Delis D. C. (2000): Neurocognitive functioning of adolescents: Effects of protracted alcohol use. *Alcohol Clin Exp Res*. 24(2): 164-171.
10. Caster J. M., Walker Q. D., Kuhn C. M. (2005): Enhanced behavioral response to repeated dose cocaine in adolescent rats. *Psychopharmacology*. 183(2): 218-225.
11. Cerniglia L., Cimino S., Ballarotto G., Casini E., Ferrari A., Carbone P., Cersosimo M. (2015): Motor vehicle accidents and adolescents: an empirical study on their emotional and behavioral profiles, defense strategies and parental support. *Transp Res Part F Traffic Psychol Behav*. 35: 28-36.
12. Cerniglia L., Cimino S., Ballarotto G., Monniello G. (2014): Parental loss during childhood and outcomes on adolescents' psychological profiles: a longitudinal study. *Curr Psychol*. 33(4): 545-556.
13. Cimino S., Cerniglia L., Paciello M. (2015): Mothers with depression, anxiety or eating disorders: Outcomes on their children and the role of paternal psychological profiles. *Child Psychiatry Hum Dev*. 46(2): 228-236.
14. Croft R. J., Mackay A. J., Mills A. T., Gruzelier J. G. (2001): The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology*. 153(3): 373-379.
15. Davis P. E., Liddiard H., McMillan T. M. (2002): Neuropsychological deficits and opiate abuse. *Drug Alcohol Depend*. 67(1): 105-108.
16. Dikmen S. S., Corrigan J. D., Levin H. S., Machamer J., Stiers W., Weisskopf M. G. (2009): Cognitive outcome following traumatic brain injury. *J Head Trauma Rehabil*. 24(6): 430-438.
17. Ersche K. D., Clark L., London M., Robbins T. W., Sahakian B. J. (2006): Profile of executive and memory function associated with amphetamine and opiate dependence. *Neuropsychopharmacology*. 31(5): 1036-1047.
18. Ersche K. D., Sahakian B. J. (2007): The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychol Rev*. 17(3): 317-336.
19. Evans G. W., Schamberg M. A. (2009): Childhood poverty, chronic stress, and adult working memory. *Proc Natl Acad Sci USA*. 106(16): 6545-6549.
20. Fishbein D. H., Krupitsky E., Flannery B. A., Langevin D. J., Bobashev G., Verbitskaya E., Augustine C.B., Bolla K.I., Zvartau E., Schech B., Egorova V., Bushara N., and Tsoyb M. (2007): Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. *Drug Alcohol Depend*. 90(1): 25-38.
21. Frank D. A., Rose-Jacobs R., Crooks D., Cabral H. J., Gerteis J., Hacker K. A., Martin B., Weinstein Z.B., Heeren T. (2011): Adolescent initiation of licit and illicit substance use: impact of intrauterine exposures and post-natal exposure to violence. *Neurotoxicol Teratol*. 33(1): 100-109.
22. Giancola P. R., Mezzich A. C., Tarter R. E. (1998): Executive cognitive functioning, temperament, and antisocial behavior in conduct-disordered adolescent females. *J Abnorm Psychol*. 107(4): 629-641.
23. Gogtay N., Giedd J. N., Lusk L., Hayashi K. M., Greenstein D., Vaituzis A. C., Nugent III T.F, Herman D.H., Clasen L.S., Toga A.W., Rapoport J.L., Thompson P.M. (2004): Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA*. 101(21): 8174-8179.
24. Gogtay N., Thompson P. M. (2010): Mapping gray matter development: implications for typical development and vulnerability to psychopathology. *Brain Cogn*. 72(1): 6-15.
25. Gruber S. A., Sagar K. A., Dahlgren M. K., Racine M., Lukas S. E. (2012): Age of onset of marijuana use and executive function. *Psychol Addict Behav*. 26(3): 496-506. .
26. Hackman D. A., Farah M. J. (2009): Socioeconomic status

and the developing brain. *Trends Cogn Sci*. 13(2): 65-73.
27. Hanson K. L., Medina K. L., Padula C. B., Tapert S. F., Brown S. A. (2011): Impact of adolescent alcohol and drug use on neuropsychological functioning in young adulthood: 10-year outcomes. *J Child Adolesc Subst Abuse*. 20(2): 135-154.
28. Harvey M. A., Sellman J. D., Porter R. L., Frampton C. M. (2007): The relationship between non-acute adolescent cannabis use and cognition. *Drug Alcohol Rev*. 26(3): 309-319.
29. Jacobsen L. K., Mencl W. E., Pugh K. R., Skudlarski P., Krystal J. H. (2004): Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. *Psychopharmacology*. 173(3-4): 383-390.
30. Kerstetter K. A., Kantak, K. M. (2007): Differential effects of self-administered cocaine in adolescent and adult rats on stimulus–reward learning. *Psychopharmacology*. 194(3): 403-411.
31. Latvala A., Castaneda A. E., Perälä J., Saarni S. I., Aalto-Setälä T., Lönnqvist J., Kaprio J., Suvisaari J., Tuulio-Henriksson A. (2009): Cognitive functioning in substance abuse and dependence: a population-based study of young adults. *Addiction*. 104(9): 1558-1568.
32. Lee S. S., Humphreys K. L., Flory K., Liu R., Glass K. (2011): Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev.* 31(3): 328-341.
33. Li M., Tian J., Zhang R., Qiu Y., Wen X., Ma X., Wang J., Xu Y., Jiang G., Huang R. (2014): Abnormal cortical thickness in heroin-dependent individuals. *Neuroimage.* 88: 295-307.
34. Lisdahl K. M., Price J. S. (2012): Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults. *J Int Neuropsychol Soc*. 18(04): 678-688.
35. Lisdahl K.M., Gilbart E.R., Wright N.E., Shollenbarger S. (2013): Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Front Psychiatry*. 4(53): 1-19.
36. Lyvers M., Yakimoff M. (2003): Neuropsychological correlates of opioid dependence and withdrawal. *Addict Behav.* 28(3): 605-611.
37. Magura S., Kang S. Y. (1996): Validity of self-reported drug use in high risk populations: a meta-analytical review. *Subst Use Misuse*. 31(9): 1131-1153.
38. Medina K. L., Schweinsburg A. D., Cohen-Zion M., Nagel B. J., Tapert S. F. (2007): Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol*. 29(1): 141-152.
39. Mezzacappa E. (2004): Alerting, orienting, and executive attention: Developmental properties and sociodemographic correlates in an epidemiological sample of young, urban children. *Child Dev.* 75(5): 1373-1386.
40. Minnes S., Singer L. T., Min M. O., Lang A. M., Ben-Harush A., Short E., Wu M. (2014): Comparison of 12-year-old children with prenatal exposure to cocaine and non-exposed controls on caregiver ratings of executive function. *J Youth Adolesc.* 43(1): 53-69.
41. Mondini S., Mapelli D., Vestri A., Arcara A., Bisiacchi P.S. (2011*): Esame neuropsicologico breve 2* (ENB-2). Raffaello Cortina Editore, Milano.
42. Mondini S., Mapelli D., Vestri A., Bisiacchi P. S. (2003): *Esame neuropsicologico breve*. Raffaello Cortina Editore, Milano.
43. Morgan C. J., Muetzelfeldt L., Curran H. V. (2009): Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*. 104(1): 77-87.
44. Morgan C. J., Muetzelfeldt L., Curran H. V. (2010): Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction*. 105(1): 121-133.
45. Moss H. B., Kirisci L., Gordon H. W., Tarter R. E. (1994): A neuropsychologic profile of adolescent alcoholics. *Alcohol Clin Exp Res*. 18(1): 159-163.
46. Ornstein T. J., Iddon J. L., Baldacchino A. M., Sahakian B. J., London M., Everitt B. J., Robbins T. (2000): Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology*. 23(2): 113-126.
47. Paciello M., Fida R., Tramontano C., Cole E., Cerniglia L. (2013): Moral dilemma in adolescence: The role of values, prosocial moral reasoning and moral disengagement in helping decision making. *Eur J Dev Psychol*. 10(2): 190-205.
48. Passetti F., Clark L., Mehta M. A., Joyce E., King M. (2008): Neuropsychological predictors of clinical outcome in opiate addiction. *Drug Alcohol Depend.* 94(1): 82-91.
49. Pau C. W., Lee T., Chan S. F. F. (2002): The impact of heroin on frontal executive functions. *Arch Clin Neuropsychol.* 17(7): 663-670.
50. Pezawas L., Fischer G., Podreka I., Schindler S., Brucke T., Jagsch R., . . . Kasper S. (2002): Opioid addiction changes cerebral blood flow symmetry. *Neuropsychobiology.* 45(2): 67-73.
51. Pope H. G., Yurgelun-Todd D. (1996): The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 275(7): 521-527.
52. Robison A. J., Nestler E. J. (2011): Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci.* 12(11): 623-637.
53. Rose-Jacobs R., Soenksen S., Appugliese D. P., Cabral H. J., Richardson M. A., Beeghly M., ... Frank D. A. (2011): Early adolescent executive functioning, intrauterine exposures and own drug use. *Neurotoxicol Teratol.* 33(3): 379-392.
54. Solowij N., Pesa N. (2010): Cognitive abnormalities and cannabis use. *Rev Bras Psiquiatr*. 32: 531-540.

55. Strickland T. L., Miller B. L., Kowell A., Stein R. (1998): Neurobiology of cocaine-induced organic brain impairment: contributions from functional neuroimaging. *Neuropsychol Rev.* 8(1): 1-9.
56. Tambelli R., Cimino S., Cerniglia L., Ballarotto G. (2015): Early maternal relational traumatic experiences and psychopathological symptoms: a longitudinal study on mother-infant and father-infant interactions. *Sci Rep*. 5: 13984.
57. Tarter R. E., Mezzich A. C., Hsieh Y. C., Parks S. M. (1995): Cognitive capacity in female adolescent substance abusers. *Drug Alcohol Depend.* 39(1): 15-21.
58. Tapert S. F., Granholm E., Leedy N. G., Brown S. A. (2002): Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *J Int Neuropsychol Soc*. 8(7): 873-883.
59. Thoma R. J., Monnig M. A., Lysne P. A., Ruhl D. A., Pommy J. A., Bogenschutz M., **[…]** Yeo R. A. (2011): Adolescent substance abuse: the effects of alcohol and marijuana on neuropsychological performance. *Alcohol Clin Exp Res.* 35(1): 39-46.
60. Verdejo-García A., Pérez-García M. (2007): Profile of executive deficits in cocaine and heroin poly-substance users: common and differential effects on separate executive components. *Psychopharmacology*. 190(4): 517-530.
61. Verdejo-García A., Perales J. C., Pérez-García M. (2007): Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav.* 32(5): 950-966.
62. Wetherill R., Tapert S. F. (2013): Adolescent Brain Development, Substance Use, and Psychotherapeutic Change. *Psychol Addict Behav.* 27(2): 393-402.
63. Zakharova E., Wade D., Izenwasser S. (2009): Sensitivity to cocaine conditioned reward depends on sex and age. *Pharmacol Biochem Behav*. 92(1): 131-134.

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Conflict of interest

Authors state no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study does not require ethics committee approval because it was carried out according to a non-interventional protocol. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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